

# Delayed Respiratory Depression with Fentanyl

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Fentanyl (Sublimaze)<sup>®</sup> is an exceptionally potent synthetic narcotic analgesic reported to be 150 times more potent than morphine.<sup>5</sup> The rapid onset and short duration of its sedative action have led to its wide use for intravenous conscious sedation in dental practice.<sup>4</sup> A recent report<sup>1</sup> of several cases of delayed respiratory depression following the use of fentanyl prompted a review of the literature dealing with the clinical effects of the drug.

In comparing the effects of several narcotic analgesics in combination with droperidol for the production of neuroleptanesthesia, Foldes et al.<sup>7</sup> noted that the duration of analgesia produced by fentanyl, meperidine and alphaprodine (Nisentil)<sup>®</sup> were similar, but the intensity and/or duration of the hypnotic effect of fentanyl was less than that of the other two narcotics.<sup>11</sup> Holmes<sup>13</sup> reported similar results with regard to the duration of the analgesic action of fentanyl, finding it no different than morphine in this respect. In reviewing a series of 584 cases of general anesthesia employing intravenous fentanyl, Grell et al.<sup>10</sup> observed that the hypnotic or euphoric effects of up to 0.8mg of the narcotic lasted only 30 to 40 minutes.

With regard to respiratory depression, Downes et al.<sup>6</sup> compared fentanyl (0.1 and 0.2 mg/kg) with 75 mg/kg of meperidine. Mean values in six normal adult volunteers for minute volume, tidal volume, and respiratory rate remained significantly below control 4 hours after intramuscular administration of both drugs. More sensitive measures of respiratory depression (ventilatory response to  $\text{CO}_2$ :  $\Delta \text{VI}/\Delta \text{Pco}_2$ ) have substantiated the prolonged effects of fentanyl on respiration. Following intravenous doses of 1.3  $\mu\text{g}/\text{kg}$  of the drug in 8 adult volunteers, Rigg and Goldsmith<sup>14</sup> showed respiratory responses to  $\text{CO}_2$  remained less than 80% of control 4 hours after drug administration. In a similar study, Harper et al.<sup>11</sup> also noted respiratory depression up to 4 hours in 10 volunteers following intravenous doses of fentanyl ranging between 1.5 and 9.0  $\mu\text{g}/\text{kg}$ . An important observation in this study was

that maximum respiratory depression occurred 5 minutes after the injection of all doses. Becker et al.<sup>3</sup> noted a biphasic pattern to  $\text{CO}_2$  response curves in 26 of 29 patients receiving fentanyl to supplement general anesthesia. Recovery appeared complete 2 hours after the final increment of fentanyl. However, three hours after the last dose, the average slope of the  $\text{CO}_2$  response curve had fallen to 55% of control.

Examination of clinical reports concerning the use of fentanyl are at variance with the widely held belief that the drug has a short (30-40 min) duration of action.<sup>2,5,9</sup> The respiratory depressant effects and perhaps the analgesic properties of the drug are evident for 3 to 4 hours.

The dissociation between the duration of analgesia (and respiratory depression) and the hypnotic effects of fentanyl, first noted by Foldes et al.<sup>7</sup> could be explained if the metabolite(s) of the narcotic had analgesic and respiratory depressant effects but lacked the hypnotic properties of the parent compound. This is suggested in the pharmacokinetic study of tritiated fentanyl in man reported by Hess et al.<sup>12</sup>

Following intravenous injection, there is a rapid decrease in plasma levels of fentanyl in the first 10-20 minutes. However, "the total radioactivity (fentanyl and metabolites) shows a tendency to rise smoothly, stay at higher levels until about 3 hours, and then decline, too." If such an explanation is valid, the fentanyl metabolites have pharmacological properties similar to methadone.<sup>9</sup>

Clinically, a prolonged period of analgesia extending beyond the brief sedative effects of fentanyl is a useful property in dental sedation, particularly for short oral surgical procedures. However, a prolonged period of respiratory depression is to be expected and will become increasingly significant if the drug is given at repeated intervals. An otherwise minor degree of airway obstruction could be hazardous to patients who have little ventilatory response to such a  $\text{CO}_2$  challenge.<sup>1</sup>

†Awarded "Honorable Mention"  
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